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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#21
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9/18/01

In re Application of	)
Edmond Daniel Roussel et al.	) Group Art Unit: 1651
Serial No.: 09/331,554	)
Filed: August 23, 1999	) Examiner: V. Afremova
Title: ABSORBABLE COMPOSITION CONTAINING PROPIONIC BACTERIA CAPABLE OF RELEASING NITRIC OXIDE IN THE HUMAN OR ANIMAL ALIMENTARY CANAL	)

BRIEF ON APPEAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Appeal Brief is submitted in support of the Notice of Appeal filed on May 7, 2001, and received by the Patent and Trademark Office on May 10, 2001. The period for submission of this Appeal Brief has been extended by two (2) months, from July 10, 2001, to September 10, 2001, by the Petition for Extension of Time under 37 CFR 1.136(a) and accompanying fee under 37 CFR 1.17(a)(2) filed concurrently herewith.

REAL PARTY IN INTEREST

The real party in interest is Laboratories Standa S.A., a corporation of France having a principal place of business at 68, rue Robert Kaskoreff, 14050 Caen Cedex, France.

RELATED APPEALS AND INTERFERENCES

There are no related cases involved in any appeal procedures or interferences.

STATUS OF CLAIMS

No claims have been allowed. Claims 13-32 stand under final rejection. Claims 1-12, 17, 18, 2, 23, 27, 28, 31 and 32 have been canceled. Claims 13-16, 19-21, 24-26, 29 and 30 (claims 15 and 25 of which were amended in the Amendment After Final Rejection filed May 7, 2001) are now the only claims pending and are the claims being appealed.

STATUS OF AMENDMENTS

Responsive to the Final Office Action dated February 7, 2001, Appellants filed an Amendment After Final Rejection on May 7, 2001, concurrently with the Notice of Appeal. That Amendment canceled claims 17, 18, 22, 23, 27, 28, 31 and 32, and amended claims 15 and 25. Responsive to the May 7 Amendment, an Advisory Action was issued on July 7, 2001, in which the Examiner maintained the rejection of claims 13-32.

A supplemental Amendment to the specification, merely providing an address for INRA-LRTL, was filed on July 5, 2001. Responsive to the July 5 supplemental Amendment, an Advisory Action was issued on July 27, 2001, in which the Examiner maintained the rejection of claims 13-32.

The Declaration of Professor Alain Ourry, Head of Department UMR INRA-UCBN 950 and Member of the Scientific Committee of Caen University, traversing the rejections of the pending claims, was submitted under 37 CFR § 1.132 on July 31, 2001.

SUMMARY OF INVENTION

The present invention is directed to an absorbable common food composition or absorbable dietary or medicinal composition containing propionibacteria which releases physiologically significant amounts nitric oxide (NO) gas in the digestive tract of a human or animal using the natural route of food metabolism. As noted in the specification at page 2, lines 13-14, no means for achieving this result has been previously proposed. Rather, as noted at page 1, line 28 through page 2, line 7, relatively small amounts of NO are produced by biosynthesis in a human or animal body from the amino acid L-arginine by a group of enzymes known as NO-synthases (NOS), of which two main types exist: constituent NOSs, which are expressed in endothelial cells; and inducible NOSs, which are expressed mainly by certain cells of the immune system.

Referring to page 2, lines 16-22, it has been discovered that a specific type of bacteria, propionibacteria, is capable of producing NO, and that certain strains and species of this bacteria type produce NO in large amounts. Thus the invention relates to the use of propionibacteria to produce absorbable food, dietary or medical compositions capable of releasing physiologically significant amounts of NO into the digestive tract. These absorbable compositions may comprise more than 10^9 cells/gram of propionibacteria, as noted at page 4, lines 8-10, and page 19, line 38 through page 20, line 6.

Referring now to page 4, lines 11-25, through various experiments described in the specification the quite specific abilities of different strains of propionibacteria to produce NO during their culturing were confirmed. Further, during and through these experiments it was discovered that the amino acid arginine is not a determining factor in the observed production of NO. As noted above, in a human or animal body, relatively small amounts of NO are produced by biosynthesis from the amino acid L-arginine by NOS enzymes.

Moreover, with reference to page 20, lines 23-26, the inventive composition can include, in addition to propionibacteria, other bacteria such as bifidobacteria and/or lactic acid bacteria. Food products to which the bacteria may be added in accordance with the present invention include, with reference to page 3, lines 12-26, cheese, sources of dietary fibre, fermented milk, dessert cream, cake and tonic drink.

ISSUES

I. Is independent claim 13 or 20, or dependent claim 21, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 4,379,170 (Hettinga et al.),** which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein?

II. Is independent claim 13 or 20, or dependent claim 21, calling for a composition, or method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal

functions, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract?

III. Is independent claim 13 or 20, or dependent claim 21, calling for a composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, unpatentable under **35 U.S.C. § 103(a)** over a combination of the disclosures of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2×10^9 cells per gram of P16, 1.2×10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest NO being synthesized by propionibacteria or by any of the processes described therein; **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract; and **Balows et al.**, which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO?

IV. Is dependent claim 14, calling for a composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, the propionibacteria, after cultivating for at least 72 hours in a Yeast Extract Lactate (YEL) medium containing at least 550 μmol/liter of nitrate, being capable of releasing at least 5 μg of nitric oxide into a human or animal digestive tract for improving intestinal functions, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which fails to teach or suggest anything whatsoever regarding cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria, at any stage of the disclosed cheese making process, being capable of releasing any quantity of nitric oxide?

V. Is dependent claim 14, calling for a composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, the propionibacteria, after cultivating for at least 72 hours in a Yeast Extract Lactate (YEL) medium containing at least 550 μmol/liter of nitrate, being capable of releasing at least 5 μg of nitric oxide into a human or animal digestive tract for improving intestinal functions, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which neither teaches nor suggests a YEL medium containing nitrate, or a propionibacteria which, after cultivation in the YEL medium, is capable of releasing any quantity of nitric oxide, particularly in a human or animal digestive tract?

VI. Is dependent claim 14, calling for composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, the propionibacteria, after cultivating for at least 72 hours in a Yeast Extract Lactate (YEL) medium containing at least 550 μmol/liter of nitrate, being capable of releasing at least 5 μg of nitric oxide into a human or animal digestive tract for improving intestinal functions, unpatentable under **35 U.S.C. § 103(a)** over a combination of the disclosures of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which fails to teach or suggest anything whatsoever regarding cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria, at any stage of the disclosed cheese making process, or the propionibacteria being capable of releasing any quantity of nitric oxide; **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium

containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which neither teaches nor suggests a YEL medium containing nitrate, or a propionibacteria which, after cultivation in the YEL medium, is capable of releasing any quantity of nitric oxide, particularly in a human or animal digestive tract; and **Balows et al.**, which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO?

VII. Is independent claim 25, or dependent claim 15 or 26, calling for a composition, or a method for making a food composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, and the composition being added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2×10^9 cells per gram of P16, 1.2×10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein?

VIII. Is independent claim 25, or dependent claim 15 or 26, calling for a composition, or a method for making a food composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal

functions, and the composition being added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which does not teach or suggest that a propionibacteria capable of releasing a physiologically significant amount of nitric oxide be added to a food product?

IX. Is independent claim 25, or dependent claim 15 or 26, calling for a composition, or a method for making a food composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, and the composition being added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink, unpatentable under **35 U.S.C. §103(a)** over a combination of the disclosures of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2×10^9 cells per gram of P16, 1.2×10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein; **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which does not teach or suggest that a propionibacteria capable of releasing a physiologically significant amount of nitric oxide be added to a food product; and **Balows et al.**, which teaches propionibacteria are commonly used as starter cultures and can grow on media with nitrate,

and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO?

X. Is dependent claim 16 or 24, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, the supplement being a dehydrated preparation, fermented liquid preparation or unfermented liquid preparation, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180° F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2×10^9 cells per gram of P16, 1.2×10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124° F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein?

XI. Is dependent claim 16 or 24, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, the supplement being a dehydrated preparation, fermented liquid preparation or unfermented liquid preparation, unpatentable under **35 U.S. § 102(b)** over the disclosure of **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which has been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract?

XII. Is dependent claim 16 or 24, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, the supplement being a dehydrated preparation, fermented liquid preparation or unfermented liquid preparation, unpatentable under **35 U.S.C. § 103(a)** over a combination of the disclosures of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180° F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2×10^9 cells per gram of P16, 1.2×10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124° F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein; **U.S. Patent No. 5,573,947 (Madec et al.)**, which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which has been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract; and **Balows et al.**, which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO?

XIII. Is independent claim 19 or 29, or dependent claim 30, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria or an amount of propionibacteria sufficient to release a physiologically significant amounts of nitric oxide into a human or animal digestive tract, and a quantity of bifidobacteria and/or lactic acid bacteria, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which teaches a Swiss or Emmental cheese being prepared by a

process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream and a culture of 0.002% lactobacillus bulgaricus, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein?

XIV. Is independent claim 19, calling for a composition for use as an absorbable dietary supplement comprising a sufficient quantity of propionibacteria and bifidobacteria and/or lactic acid bacteria, the composition capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract, unpatentable under **35 U.S.C. § 102(b)** over the disclosure of **U.S. Patent No. 5,573,947 (Madec et al.)**, which discloses a culture medium in which propionic bacteria may be specifically counted, but which fails to teach or suggest the release of nitric oxide by propionibacteria, alone or in combination with bifidobacteria and/or lactic acid bacteria, particularly in a human or animal digestive tract?

XV. Is independent claim 19 or 29, or dependent claim 30, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria or an amount of propionibacteria sufficient to release a physiologically significant amounts of nitric oxide into a human or animal digestive tract, and a quantity of bifidobacteria and/or lactic acid bacteria, unpatentable under **35 U.S.C. § 103(a)** over a combination of the disclosures of **U.S. Patent No. 4,379,170 (Hettinga et al.)**, which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream and a culture of 0.002% lactobacillus bulgaricus, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein; **U.S. Patent No. 5,573,947 (Madec et al.)**, which discloses a culture medium in which propionic bacteria may be specifically counted, but which fails to teach or suggest the

release of nitric oxide by propionibacteria, alone or in combination with bifidobacteria and/or lactic acid bacteria, particularly in a human or animal digestive tract; and **Balows et al.**, which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO?

GROUPING OF CLAIMS

A. Claims 13, 14, 16, 20, 21 and 24 stand or fall together.

B. Claims 15, 25 and 26 stand or fall together.

C. Claims 19, 29 and 30 stand or fall together.

Claim Group A.:

Independent claim 13 recites that a composition for use as an absorbable dietary supplement for human and animal consumption comprises more than 10^9 cells/gram propionibacteria, that propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into the digestive tract.

Dependent claim 14, which depends from independent claim 13, recites that in the composition, the propionibacteria is capable of releasing at least 5 μg of nitric oxide.

Dependent claim 16, which depends from independent claim 13, recites that the supplement is a preparation of the form selected from the list of dehydrated, fermented liquid and unfermented liquid preparations.

Independent claim 20 recites that a method for making a composition for use as a dietary supplement includes selecting, from a provided supply of propionibacteria, an amount thereof sufficient to release physiologically significant amounts of nitric oxide into the digestive tract.

Dependent claim 21, which depends from independent claim 20, recites that more than 10^9 cells/gram propionibacteria be selected.

Dependent claim 24, which depends from independent claim 20, recites that the supplement be formed into one of the group consisting of a dehydrated preparation, a fermented liquid preparation, or an unfermented preparation.

The limitations of claims 13, 14, 16, 20, 21 and 24 are believed to distinguish over the art as discussed below, and render them separately patentable relative to the other pending

claims. Accordingly, these claims do not stand or fall together with the other appealed claims.

Claim Group B.:

Dependent claim 15, which depends from independent claim 13, recites that a composition for use as an absorbable dietary supplement for human and animal consumption comprising more than 10^9 cells/gram propionibacteria, that propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into the digestive tract, is added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake and tonic drink.

Independent claim 25 recites that a method for making a food composition for use as a dietary supplement includes selecting, from a provided supply of propionibacteria, an amount thereof sufficient to release physiologically significant amounts of nitric oxide into the digestive tract, and adding the propionibacteria to a provided food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink.

Dependent claim 26, which depends from independent claim 25, recites that in making the food composition, more than 10^9 cells/gram propionibacteria be selected.

The limitations of claims 15, 25 and 26 are believed to distinguish over the art as discussed below, and render them separately patentable relative to the other pending claims. Accordingly, these claims do not stand or fall together with the other appealed claims.

Claim Group C.:

Independent claim 19 recites that a composition for use as an absorbable dietary supplement for human and animal consumption comprise a sufficient quantity of propionibacteria and one or more selected from the group consisting of bifidobacteria and lactic acid bacteria, and that the composition be capable or releasing a physiologically sufficient amount of nitric oxide into the digestive tract.

Independent claim 29 recites that a method for making a composition for use as a dietary supplement includes providing a supply of propionibacteria and at least one of the group of bifidobacteria and lactic acid bacteria, and selecting an amount of propionibacteria sufficient to release physiologically significant amounts of nitric oxide into the digestive tract.

Dependent claim 30, which depends from independent claim 29, recites that more than 10^9 cells/gram propionibacteria be selected.

The limitations of claims 19, 29 and 30 are believed to distinguish over the art as discussed below, and render them separately patentable relative to the other pending claims. Accordingly, these claims do not stand or fall together with the other appealed claims.

REFERENCES

The following references have been relied upon by the Examiner:

Hettinga et al.	4,379,170	April 5, 1983
Madec et al.	5,573,947	November 12, 1996

1 The Prokaryotes 554-556, 834-849 (Balows et al. eds., 2d ed. 1992)

BRIEF DESCRIPTION OF THE REFERENCES

Hettinga et al. '170 is directed to a process for the manufacture of a Swiss or Emmental flavored cheese product in which a mixture containing skim milk is fermented with 80 ppm of Rhozyme P-11 and 6.6% inoculum of a 50/50 mixture of Propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cell/gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours. This mixture is combined with a pasteurized skim milk concentrate and pasteurized cream, and then the mixture is cooked at 124° F for 20 minutes. This reference does not teach or suggest, however, that NO may be synthesized by propionibacteria or by any of the processes described therein. None of the chemical analyses of bacteria proliferation media detailed in the 14 examples provided in this reference quantify or consider the precursor compounds needed for NO synthesis.

Madec et al. '947 is directed to a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions. This reference also discloses a comparative YELA reference medium to which as been added a culture of propionic bacteria with a concentration of 2.6 x 10^9 cells/ml. This reference does not teach or suggest, however, the production of NO by these bacteria, particularly not in a human or animal digestive tract. Further, this reference does not teach or consider the nitrogen sources, and more specifically the nitrate or nitrite substrate needed for NO synthesis.

Balows et al. teaches generally that propionibacteria are commonly used as starter cultures and can grow on media with nitrate. Balows et al. also teaches that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or

nitrous oxide. The portions of this reference cited by the Examiner do not disclose experimental data demonstrating that propionibacteria are able to produce NO. The only cited portion of this reference which considers the production of NO molecules by bacteria is from Chapter 23, entitled "The Denitrifying Prokaryotes." Here, at page 556, second paragraph, the reference mentions that "[w]hether a true respiratory utilization of nitrite by the fermentative Propionibacterium occurs, has been questioned; it may instead be a detoxification process (Kaspar, 1982)."

In the Declaration submitted under 37 CFR § 1.132 on July 31, 2001, Professor Alain Ourry, Head of Department UMR INRA-UCBN 950 and Member of the Scientific Committee of Caen University, also discusses at length what is, and what is not, taught by each of the above references.

THE REJECTIONS

Under 35 U.S.C. § 102(b) over U.S. Patent No. 4,379,170:

Independent claims 13, 19, 20, 25 and 29 and dependent claims 14-16, 21, 24, 26 and 30 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,379,170 to Hettinga. In the Final Office Action dated February 7, 2001, the Examiner states that this reference is relied upon as explained in the prior office action (dated July 26, 2000). There the Examiner stated that "[a]lthough the reference is silent with regard to ability of particular strains P16 and P20 to release nitric oxide at particular amounts at particular conditions, the cited compositions are considered to inherently possess ability to release nitric oxide since the cited bacteria belong to the same bacteria genus and they are used for the same purpose of preparing dietary compositions such as cheese at the same amounts as required by the presently claimed composition and method of making the claimed dietary composition." (Emphasis added.)

Moreover, the Examiner contends that the reference teaches the use of the strain P20 in a food product, and that according to the disclosure of the present application, P20 is capable of releasing nitric oxide.

Under 35 U.S.C. § 102(b) over U.S. Patent No. 5,573,947:

Independent claims 13, 20 and 25 and dependent claims 14, 15, 16, 21, 24 and 26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,573,947 to Madec et al. In the Final Office Action dated February 7, 2001, the Examiner states that this reference is relied upon as explained in the prior office action (dated July 26, 2000). There

the Examiner stated that "[a]lthough the reference is silent with regard to ability of particular strains to release nitric oxide at particular amounts at particular conditions, the cited compositions/methods are considered to inherently possess the identical characteristics as presently claimed compositions/methods since the cited propionibacteria, which substitute [sic] the major component of the cited compositions and methods, belong to identical bacteria strains as applicants' strains." (Emphasis added.)

Under 35 U.S.C. § 103(a) over U.S. Patents Nos. 4,379,170 and 5,573,947, and the disclosure of Balows et al.:

Independent claims 13, 19, 20, 25 and 29 and dependent claims 14-16, 21, 24, 26 and 30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,379,170 to Hettinga et al., U.S. Patent No. 5,573,947 to Madec et al. and the disclosure of Balows et al.

Hettinga et al. '170 is relied upon by the Examiner as explained above. The Examiner contends that it discloses a dietary composition/method for making the composition with propionibacteria and lactic bacteria, and a dietary composition/method of making the composition with propionibacteria and lactic bacteria, but the Examiner concedes that it is lacking a particular disclosure with regard to the use of particular strains belonging to *P. acidipropionici* and to *P. freudenreichii.*

Madec et al. '947 is relied upon by the Examiner merely for disclosing particular strains belonging to *P. acidipropionici* and to *P. freudenreichii.*

Balows et al. is relied upon by the Examiner for teaching an important role of propionibacteria in the cheese industry wherein propionibacteria known as *P. acidipropionici* and *P. freudenreichii* are taught to be commonly used as starter cultures. Additionally, the reference is relied upon for teaching the ability of propionibacteria to grow on media with nitrate and supposedly characterizing propionibacteria as denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide wherein nitric oxide is an intermediate product of denitrifying bacteria including *Propionibacteria sp.*

The Examiner asserts that it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the composition and methods for making the composition disclosed in Hettinga et al. '170 by using particular strains of the bacteria disclosed in Madec et al. '947 with a reasonable expectation of success in producing a dietary composition because propionibacteria are commonly used in cheesemaking and they

are known to produce gaseous products during fermentation in the media comprising nitrates, as taught by Balows et al. Therefore, the Examiner contends, the claimed invention as a whole is clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The Examiner also asserts that Hettinga et al. '170 teaches the incorporation into a food composition of identical amounts such as 6.2×10^9 plus 1.2×10^9 cells per gram, which is more than the claimed amount of 10^9 cells per gram, and therefore Appellants's previously made argument directed toward the idea that propionibacteria in the cited references are not present in compositions in particular amounts which would allow for release of nitric oxide in physiologically sufficient amounts are not convincing.

Further, the Examiner asserts that Madec et al. '947 teaches the use of identical strains at similar, if not identical, concentrations of 10^9 cells per gram of a composition, and draws the conclusion that amounts of nitric oxide are reasonably expected to be released in identical, if not similar, physiological amounts as the presently claimed compositions, particularly in view that denitrifying bacteria, supposedly including propionibacteria, are known to release nitric oxide as intermediate product during reduction of nitrates.

ARGUMENTS

I. None of independent claims 13 and 20, and dependent claim 21, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, is unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2×10^9 cells per gram of P16, 1.2×10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the pr cesses described therein.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 13, 20 or 21 is not expressly described in Hettinga et al. '170. This reference in no way teaches or suggests, let alone expressly describes, that NO may be synthesized by propionibacteria or by any of the processes described therein.

Nor is it necessary and inevitable that, in the disclosed cheesemaking process, the propionibacteria release a physiologically significant amount of NO into a human or animal digestive tract, and therefore Hettinga et al. '170 also fails to inherently describe each and every element as set forth in any of claims 13, 20 and 21. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

Further, as Professor Ourry explains in Paragraph 7 of the Declaration filed July 31, 2001: "No mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

For these reasons, Appellants submit that claims 13, 20 and 21 distinguish over Hettinga et al. '170 and, because each and every element set forth in any of claims 13, 20 and 21 is not expressly or inherently described in this reference, none of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of these rejections.

II. None of independent claims 13 and 20, and dependent claim 21, calling for a composition, or method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, is unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 13, 20 or 21 is not expressly described in Madec et al. '947. This reference in no way teaches or suggests, let alone expressly describes, the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract.

Nor is it necessary and inevitable that the propionibacteria being counted through use of the disclosed medium releases nitric oxide, and certainly not in a human or animal digestive tract, and therefore Madec et al. '947 also fails to inherently describe each and every element as set forth in any of claims 13, 20 and 21. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 8 of the Declaration filed July 31, 2001: "Although considering extensively in the introduction section all the potential use of

Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

For these reasons, Appellants submit that claims 13, 20 and 21 distinguish over Madec et al. '947 and, because each and every element set forth in any of claims 13, 20 and 21 is not expressly or inherently described in this reference, none of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of these rejections.

III. None of independent claims 13 and 20, and dependent claim 21, calling for a composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, is unpatentable under 35 U.S.C. § 103(a) over a combination of the disclosures of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest NO being synthesized by propionibacteria or by any of the processes described therein; U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6 x 10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract; and Balows et al., which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous

oxide, but which fails to provide any direct or indirect evidence that can be used t suggest that propionibacteria have the capacity to synthesize NO.

"Obviousness cannot be established by combining teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so." ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (emphasis provided) (citations omitted). Appellants submit that these references provide no suggestion or incentive for combining their teachings to yield the invention claimed in any of claims 13, 20 and 21.

As noted above, Hettinga et al. '170 in no way teaches or suggests that NO may be synthesized by propionibacteria or by any of the processes described therein, or that a physiologically significant amount of NO be released by propionibacteria into a human or animal digestive tract. With regard to Hettinga et al. '170, Professor Ourry explains, in Paragraph 7 of the Declaration filed July 31, 2001, that "[n]o mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

As also noted above, Madec et al. '947 in no way teaches or suggests the release of nitric oxide by propionibacteria, and particularly not in a human or animal digestive tract. With regard to Madec et al. '947, Professor Ourry explains, in Paragraph 8 of the Declaration filed July 31, 2001, that "[a]lthough considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

With regard to Balows et al., Appellants submit that this reference also fails to provide any suggestion of or incentive for synthesizing NO from propionibacteria. This is

verified by Professor Ourry in Paragraph 6 of the Declaration filed July 31, 2001: "[I]t is clear that the book published by Balows et al. (1992) and cited by the Examiner does not reveal or show experimental data demonstrating that Propionibacteria are able to produce NO. Chapter 23 entitled 'The Denitrifying Prokaryotes,' is the only chapter considering the production of NO molecules by bacteria. The only mention of Propionibacteria in this chapter (Page 556, second paragraph) is given as: 'Whether a true respiratory utilization of nitrite by the fermentative Propionibacterium occurs, has been questioned; it may instead be a detoxification process (Kaspar, 1982). This sentence does not explicitly mean or even suggest that Propionibacteria are able to synthesize NO. Moreover, if the Kaspar reference is analyzed, then it appears that no experimental data concerning the NO synthesis by Propionibacteria is given; the author considered *sensu stricto* the synthesis of N_2O (nitrous oxide). Although it is well known that denitrifying bacteria have the metabolic apparatus to produce NO from nitrite, it cannot be deduced from the current knowledge that Propionibacteria share the same capacity. In chapter 37 of the Balows et al. reference, the genus Propionibacterium is described: the usual known habitat of such bacteria is limited to dairy products, while denitrifying bacteria are known to be telluric organisms. Therefore, in this book there is no direct or indirect evidence that can be used to suggest that Propionibacteria have the capacity to synthesize NO like denitrifying bacteria." (Citations omitted.)

Therefore, Appellants submit, no combination of these three references may properly render any of claims 13, 21 and 21 obvious to one of ordinary skill in the art under § 103. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

Further, in traversing the appealed rejections Professor Ourry also states, in Paragraph 9 of the Declaration filed July 31, 2001, that, "[t]aken independently or even as a whole, none of the documents referred to by the Examiner provide any direct or indirect evidence to support the view that the invention proposed by applicants could be rendered obvious. None of them describes or even suggests (i) the synthesis of NO by Propionibacteria or uses a relevant reference to do so, or (ii) the use of these bacteria and their role in the digestive tract

for NO accumulation. Overall, since the production of NO by Propionibacteria and its potential accumulation have never been described under general (i.e., before their consumption) or post-consumption conditions, it cannot be deduced that there is the potential for NO production within the digestive tracts of consumers without the knowledge provided by the applicants." Moreover, Professor Ourry submits, in Paragraph 10 of the Declaration, that none of the following original results obtained through a collaboration with Appellants and which constitute the basis of the invention, can be rendered obvious from the analysis of Hettinga et al. '170, Madec et al. '947 and/or Balows et al.:

i. Certain strains of Propionibacteria are able to produce significant amounts of NO under anaerobic conditions, which can further be accumulated in the surrounding medium.

ii. Synthesis of NO by Propionibacterium cultures does not involve the well known NO synthase pathway using arginine as a precursor, but another metabolic route using nitrate or nitride as a substrate.

iii. NO synthesis by Propionibacteria can use nitrate already present in a YEL growth medium and can be further increased by the supply of nitrate and nitrite.

iv. NO synthesis by Propionibacteria is increased at physiological body temperature (37°C) relatively to temperatures normally used in vitro for growing bacteria.

v. A comparison between different strains of Propionibacteria showed that not all strains are able to produce NO, several being devoid of any capacity for NO synthesis. Some specific strains have been characterized as being able to produce much more NO than other strains.

Additionally, Appellants submit that even if there were some suggestion or incentive for combining their teachings to yield the invention claimed in claim 13, 20 or 21, nothing in the prior art references cited by the Examiner suggests the advantages to be derived from combining their teachings. "[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings." In re Sernaker, 702 F.2d 989, 995-96, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). Various advantages provided by the present invention(s), including those related to the health and energy-giving effects of nitric oxide, the means for

administering a dosage thereof, and composition shelf life, are described in pages 1-4 of the specification.

For the above reasons, Appellants submit that no combination of the cited references may properly render the inventions claimed in claims 13, 20 or 21 obvious under § 103, and respectfully request that these rejections now be reversed.

IV. Dependent claim 14, calling for a composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, the propionibacteria, after cultivating for at least 72 hours in a Yeast Extract Lactate (YEL) medium containing at least 550 μmol/liter of nitrate, being capable of releasing at least 5 μg of nitric oxide into a human or animal digestive tract for improving intestinal functions, is not unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 4,379,170 (Hettinga et al.), which fails to teach or suggest anything whatsoever regarding cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria, at any stage of the disclosed cheese making process, being capable of releasing any quantity of nitric oxide.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 14 is not expressly described in Hettinga et al. '170. This reference in no way teaches or suggests, let alone expressly describes, cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria, at any stage of the disclosed cheese making process, being capable of releasing any quantity of nitric oxide, let alone at least 5 μg of nitric oxide.

Nor is it necessary and inevitable that, in the disclosed cheesemaking process, the propionibacteria release at least 5 μg of nitric oxide, and therefore Hettinga et al. '170 also fails to inherently describe each and every element as set forth in claim 14. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 7 of the Declaration filed July 31, 2001: "No mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

For these reasons, Appellants submit that claim 14 distinguishes over Hettinga et al. '170 and, because each and every element set forth in claim 14 is not expressly or inherently described in this reference, this claim is not anticipated by this reference under § 102(b). Appellants respectfully request reversal of this rejection.

V. Dependent claim 14, calling for a composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, the propionibacteria, after cultivating for at least 72 hours in a Yeast Extract Lactate (YEL) medium containing at least 550 μmol/liter of nitrate, being capable of releasing at least 5 μg of nitric oxide into a human or animal digestive tract for improving intestinal functions, is not unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which neither teaches nor suggests a YEL medium containing nitrate, or a propionibacteria which, after cultivation in the YEL medium, is capable of releasing any quantity of nitric oxide, particularly in a human or animal digestive tract.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 14 is not expressly described in Madec et al. '947. This reference in no way teaches or suggests, let alone

expressly describes, cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria being capable of releasing any quantity of nitric oxide, let alone at least 5 μg of nitric oxide, and certainly not in a human or animal digestive tract.

Nor is it necessary and inevitable that the propionibacteria being counted through use of the disclosed medium releases 5 μg of nitric oxide, and certainly not in a human or animal digestive tract, and therefore Madec et al. '947 also fails to inherently describe each and every element as set forth in claim 14. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 8 of the Declaration filed July 31, 2001: "Although considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

For these reasons, Appellants submit that claim 14 distinguishes over Madec et al. '947 and, because each and every element set forth in claim 14 is not expressly or inherently described in this reference, this claim is not anticipated by this reference under § 102(b). Appellants respectfully request reversal of this rejection.

VI. Dependent claim 14, calling for composition for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, the propionibacteria, after cultivating for at least 72 hours in a Yeast Extract Lactate (YEL) medium containing at least 550 μmol/liter of nitrate, being capable of releasing at least 5 μg of nitric oxide into a human or animal digestive tract for improving intestinal functions, is not unpatentable under 35 U.S.C. § 103(a) over a combination of the disclosures of U.S. Patent No. 4,379,170 (Hettinga et al.), which fails to teach or suggest anything whatsoever regarding cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria, at any stage of the disclosed cheese making

process, or the propionibacteria being capable of releasing any quantity f nitric xide; U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which neither teaches nor suggests a YEL medium containing nitrate, or a propionibacteria which, after cultivation in the YEL medium, is capable of releasing any quantity of nitric oxide, particularly in a human or animal digestive tract; and Balows et al., which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO.

"Obviousness cannot be established by combining teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so." ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (emphasis provided) (citations omitted). Appellants submit that these references provide no suggestion or incentive for combining their teachings to yield the invention claimed in claim 14.

As noted above, Hettinga et al. '170 in no way teaches or suggests cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria, at any stage of the disclosed cheese making process, being capable of releasing any quantity of nitric oxide, let alone at least 5 μg of nitric oxide. With regard to Hettinga et al. '170, Professor Ourry explains, in Paragraph 7 of the Declaration filed July 31, 2001, that "[n]o mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the

consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

As also noted above, Madec et al. '947 in no way teaches or suggests cultivating a propionibacteria in a YEL medium containing nitrate, or the propionibacteria being capable of releasing any quantity of nitric oxide, let alone at least 5 μg of nitric oxide, and certainly not in a human or animal digestive tract. With regard to Madec et al. '947, Professor Ourry explains, in Paragraph 8 of the Declaration filed July 31, 2001, that "[a]lthough considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

With regard to Balows et al., Appellants submit that this reference also fails to provide any suggestion of or incentive for propionibacteria being capable of releasing at least 5 μg of nitric oxide. This is verified by Professor Ourry in Paragraph 6 of the Declaration filed July 31, 2001: "[I]t is clear that the book published by Balows et al. (1992) and cited by the Examiner does not reveal or show experimental data demonstrating that Propionibacteria are able to produce NO. Chapter 23 entitled 'The Denitrifying Prokaryotes,' is the only chapter considering the production of NO molecules by bacteria. The only mention of Propionibacteria in this chapter (Page 556, second paragraph) is given as: 'Whether a true respiratory utilization of nitrite by the fermentative Propionibacterium occurs, has been questioned; it may instead be a detoxification process (Kaspar, 1982). This sentence does not explicitly mean or even suggest that Propionibacteria are able to synthesize NO. Moreover, if the Kaspar reference is analyzed, then it appears that no experimental data concerning the NO synthesis by Propionibacteria is given; the author considered *sensu stricto* the synthesis of N_2O (nitrous oxide). Although it is well known that denitrifying bacteria have the metabolic apparatus to produce NO from nitrite, it cannot be deduced from the current knowledge that Propionibacteria share the same capacity. In chapter 37 of the Balows et al. reference, the genus Propionibacterium is described: the usual known habitat of such bacteria is limited to dairy products, while denitrifying bacteria are known to be telluric organisms. Therefore, in this book there is no direct or indirect evidence that can be used to suggest that

Propionibacteria have the capacity to synthesize NO like denitrifying bacteria." (Citations omitted.)

Therefore, Appellants submit, no combination of these three references may properly render claim 14 obvious to one of ordinary skill in the art under § 103. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

Further, in traversing the appealed rejections Professor Ourry also states, in Paragraph 9 of the Declaration filed July 31, 2001, that, "[t]aken independently or even as a whole, none of the documents referred to by the Examiner provide any direct or indirect evidence to support the view that the invention proposed by applicants could be rendered obvious. None of them describes or even suggests (i) the synthesis of NO by Propionibacteria or uses a relevant reference to do so, or (ii) the use of these bacteria and their role in the digestive tract for NO accumulation. Overall, since the production of NO by Propionibacteria and its potential accumulation have never been described under general (i.e., before their consumption) or post-consumption conditions, it cannot be deduced that there is the potential for NO production within the digestive tracts of consumers without the knowledge provided by the applicants." Moreover, Professor Ourry submits, in Paragraph 10 of the Declaration, that none of the following original results obtained through a collaboration with Appellants and which constitute the basis of the invention, can be rendered obvious from the analysis of Hettinga et al. '170, Madec et al. '947 and/or Balows et al.:

i. Certain strains of Propionibacteria are able to produce significant amounts of NO under anaerobic conditions, which can further be accumulated in the surrounding medium.

ii. Synthesis of NO by Propionibacterium cultures does not involve the well known NO synthase pathway using arginine as a precursor, but another metabolic route using nitrate or nitride as a substrate.

iii. NO synthesis by Propionibacteria can use nitrate already present in a YEL growth medium and can be further increased by the supply of nitrate and nitrite.

iv. NO synthesis by Propionibacteria is increased at physiological body temperature (37°C) relatively to temperatures normally used in vitro for growing bacteria.

v. A comparison between different strains of Propionibacteria showed that not all strains are able to produce NO, several being devoid of any capacity for NO synthesis. Some specific strains have been characterized as being able to produce much more NO than other strains.

Additionally, Appellants submit that even if there were some suggestion or incentive for combining their teachings to yield the invention claimed in claim 14, nothing in the prior art references cited by the Examiner suggests the advantages to be derived from combining their teachings. "[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings." In re Sernaker, 702 F.2d 989, 995-96, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). Various advantages provided by the present invention(s), including those related to the health and energy-giving effects of nitric oxide, the means for administering a dosage thereof, and composition shelf life, are described in pages 1-4 of the specification.

For the above reasons, Appellants submit that no combination of the cited references may properly render the invention claimed in claim 14 obvious under § 103, and respectfully request that this rejection now be reversed.

VII. None of independent claim 25, and dependent claims 15 and 26, calling for a composition, or a method for making a food composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, and the composition being added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink, is unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of

P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 15, 25 or 26 is not expressly described in Hettinga et al. '170. This reference in no way teaches or suggests, let alone expressly describes, that NO may be synthesized by propionibacteria or by any of the processes described therein. Further, this reference does not disclose a food composition which is added to a food product.

Nor is it necessary and inevitable that, in the disclosed cheesemaking process, the propionibacteria release a physiologically significant amount of NO into a human or animal digestive tract, and therefore Hettinga et al. '170 also fails to inherently describe each and every element as set forth in any of claims 15, 25 and 26. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 7 of the Declaration filed July 31, 2001: "No mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

For these reasons, Appellants submit that claims 15, 25 and 26 distinguish over Hettinga et al. '170 and, because each and every element set forth in any of claims 15, 25 and 26 is not expressly or inherently described in this reference, none of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of these rejections.

VIII. None of independent claim 25, and dependent claims 15 and 26, calling for a composition, or a method for making a food composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, and the composition being added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink, is unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which does not teach or suggest that a propionibacteria capable of releasing a physiologically significant amount of nitric oxide be added to a food product.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 15, 25 or 26 is not expressly described in Madec et al. '947. This reference in no way teaches or suggests, let alone expressly describes, the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract, or a food composition which is added to a food product.

Nor is it necessary and inevitable that the propionibacteria being counted through use of the disclosed medium releases nitric oxide, and certainly not in a human or animal digestive tract, and therefore Madec et al. '947 also fails to inherently describe each and every element as set forth in any of claims 15, 25 and 26. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is

necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 8 of the Declaration filed July 31, 2001: "Although considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

For these reasons, Appellants submit that claims 15, 25 and 26 distinguish over Madec et al. '947 and, because each and every element set forth in any of claims 15, 25 and 26 is not expressly or inherently described in this reference, none of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of these rejections.

IX. None of independent claim 25, and dependent claims 15 and 26, calling for a composition, or a method for making a food composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, and the composition being added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink, is unpatentable under 35 U.S.C. §103(a) over a combination of the disclosures of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria r

by any of the processes described therein; U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which had been added a culture of propionic bacteria with a concentration of 2.6 x 10^9 cells/ml, but which does not teach or suggest that a propionibacteria capable of releasing a physiologically significant amount of nitric oxide be added to a food product; and Balows et al., which teaches propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO.

"Obviousness cannot be established by combining teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so." ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (emphasis provided) (citations omitted). Appellants submit that these references provide no suggestion or incentive for combining their teachings to yield the invention claimed in any of claims 15, 25 and 26.

As noted above, Hettinga et al. '170 in no way teaches or suggests that NO may be synthesized by propionibacteria or by any of the processes described therein. With regard to Hettinga et al. '170, Professor Ourry explains, in Paragraph 7 of the Declaration filed July 31, 2001, that "[n]o mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

As also noted above, Madec et al. '947 in no way teaches or suggests the release of nitric oxide by propionibacteria, and particularly not in a human or animal digestive tract.

With regard to Madec et al. '947, Professor Ourry explains, in Paragraph 8 of the Declaration filed July 31, 2001, that "[a]lthough considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

With regard to Balows et al., Appellants submit that this reference also fails to provide any suggestion of or incentive for synthesizing NO from propionibacteria. This is verified by Professor Ourry in Paragraph 6 of the Declaration filed July 31, 2001: "[I]t is clear that the book published by Balows et al. (1992) and cited by the Examiner does not reveal or show experimental data demonstrating that Propionibacteria are able to produce NO. Chapter 23 entitled 'The Denitrifying Prokaryotes,' is the only chapter considering the production of NO molecules by bacteria. The only mention of Propionibacteria in this chapter (Page 556, second paragraph) is given as: 'Whether a true respiratory utilization of nitrite by the fermentative Propionibacterium occurs, has been questioned; it may instead be a detoxification process (Kaspar, 1982). This sentence does not explicitly mean or even suggest that Propionibacteria are able to synthesize NO. Moreover, if the Kaspar reference is analyzed, then it appears that no experimental data concerning the NO synthesis by Propionibacteria is given; the author considered *sensu stricto* the synthesis of N_2O (nitrous oxide). Although it is well known that denitrifying bacteria have the metabolic apparatus to produce NO from nitrite, it cannot be deduced from the current knowledge that Propionibacteria share the same capacity. In chapter 37 of the Balows et al. reference, the genus Propionibacterium is described: the usual known habitat of such bacteria is limited to dairy products, while denitrifying bacteria are known to be telluric organisms. Therefore, in this book there is no direct or indirect evidence that can be used to suggest that Propionibacteria have the capacity to synthesize NO like denitrifying bacteria." (Citations omitted.)

Therefore, Appellants submit, no combination of these three references may properly render any of claims 15, 25 and 26 obvious to one of ordinary skill in the art under § 103. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim

to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

Further, in traversing the appealed rejections Professor Ourry also states, in Paragraph 9 of the Declaration filed July 31, 2001, that, "[t]aken independently or even as a whole, none of the documents referred to by the Examiner provide any direct or indirect evidence to support the view that the invention proposed by applicants could be rendered obvious. None of them describes or even suggests (i) the synthesis of NO by Propionibacteria or uses a relevant reference to do so, or (ii) the use of these bacteria and their role in the digestive tract for NO accumulation. Overall, since the production of NO by Propionibacteria and its potential accumulation have never been described under general (i.e., before their consumption) or post-consumption conditions, it cannot be deduced that there is the potential for NO production within the digestive tracts of consumers without the knowledge provided by the applicants." Moreover, Professor Ourry submits, in Paragraph 10 of the Declaration, that none of the following original results obtained through a collaboration with Appellants and which constitute the basis of the invention, can be rendered obvious from the analysis of Hettinga et al. '170, Madec et al. '947 and/or Balows et al.:

i. Certain strains of Propionibacteria are able to produce significant amounts of NO under anaerobic conditions, which can further be accumulated in the surrounding medium.

ii. Synthesis of NO by Propionibacterium cultures does not involve the well known NO synthase pathway using arginine as a precursor, but another metabolic route using nitrate or nitride as a substrate.

iii. NO synthesis by Propionibacteria can use nitrate already present in a YEL growth medium and can be further increased by the supply of nitrate and nitrite.

iv. NO synthesis by Propionibacteria is increased at physiological body temperature (37°C) relatively to temperatures normally used in vitro for growing bacteria.

v. A comparison between different strains of Propionibacteria showed that not all strains are able to produce NO, several being devoid of any capacity for NO synthesis. Some specific strains have been characterized as being able to produce much more NO than other strains.

Additionally, Appellants submit that even if there were some suggestion or incentive for combining their teachings to yield the invention claimed in claim 15, 25 or 26, nothing in the prior art references cited by the Examiner suggests the advantages to be derived from combining their teachings. "[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings." In re Sernaker, 702 F.2d 989, 995-96, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). Various advantages provided by the present invention(s), including those related to the health and energy-giving effects of nitric oxide, the means for administering a dosage thereof, and composition shelf life, are described in pages 1-4 of the specification.

For the above reasons, Appellants submit that no combination of the cited references may properly render the inventions claimed in claims 15, 25 or 26 obvious under § 103, and respectfully request that these rejections now be reversed.

X. Neither of dependent claims 16 and 24, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, the supplement being a dehydrated preparation, fermented liquid preparation or unfermented liquid preparation, is unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180° F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124° F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 16 or 24 is not expressly described in Hettinga et al. '170. This reference in no way teaches or suggests, let alone expressly describes, that NO may be synthesized by propionibacteria or by any of the processes described therein. Further, this reference does not disclose a dietary supplement which is a dehydrated preparation, a fermented liquid preparation or a unfermented liquid preparation.

Nor is it necessary and inevitable that, in the disclosed cheesemaking process, the propionibacteria release a physiologically significant amount of NO into a human or animal digestive tract, or that a dietary supplement (the cheese) be a dehydrated preparation, a fermented liquid preparation or an unfermented liquid preparation, and therefore Hettinga et al. '170 also fails to inherently describe each and every element as set forth in either of claims 16 and 24. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 7 of the Declaration filed July 31, 2001: "No mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

For these reasons, Appellants submit that claims 16 and 24 distinguish over Hettinga et al. '170 and, because each and every element set forth in either of claims 16 and 24 is not expressly or inherently described in this reference, neither of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of these rejections.

XI. Neither of dependent claims 16 and 24, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, the supplement being a dehydrated preparation, fermented liquid preparation or unfermented liquid preparation, is unpatentable under 35 U.S. § 102(b) over the disclosure of U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which has been added a culture of propionic bacteria with a concentration of 2.6×10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 16 or 24 is not expressly described in Madec et al. '947. This reference in no way teaches or suggests, let alone expressly describes, the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract, or a dietary supplement which is a dehydrated preparation, a fermented liquid preparation or an unfermented liquid preparation.

Nor is it necessary and inevitable that the propionibacteria being counted through use of the disclosed medium releases nitric oxide, and certainly not in a human or animal digestive tract, or that a dietary supplement be a dehydrated preparation, a fermented liquid preparation or an unfermented liquid preparation, and therefore Madec et al. '947 also fails to inherently describe each and every element as set forth in either of claims 16 and 24. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set

of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 8 of the Declaration filed July 31, 2001: "Although considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

For these reasons, Appellants submit that claims 16 and 24 distinguish over Madec et al. '947 and, because each and every element set forth in either of claims 16 and 24 is not expressly or inherently described in this reference, none of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of these rejections.

XII. Neither of dependent claims 16 and 24, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria, or a sufficient amount of propionibacteria, the propionibacteria being capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive tract for improving intestinal functions, the supplement being a dehydrated preparation, fermented liquid preparation or unfermented liquid preparation, is unpatentable under 35 U.S.C. § 103(a) over a combination of the disclosures of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180° F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream, and cooking this mixture at 124° F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein; U.S. Patent No. 5,573,947 (Madec et al.), which teaches a culture medium containing lithium and polyols and/or antibiotics in which propionic bacteria from a biological sample may be specifically counted under anaerobic conditions, and discloses a comparative YELA reference medium to which has been added a culture of propionic bacteria with a concentration f 2.6 x 10^9 cells/ml, but which fails to teach or suggest the release of nitric oxide by

propionibacteria, particularly in a human or animal digestive tract; and Balows et al., which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO.

"Obviousness cannot be established by combining teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so." ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (emphasis provided) (citations omitted). Appellants submit that these references provide no suggestion or incentive for combining their teachings to yield the invention claimed in either of claims 16 and 24.

As noted above, Hettinga et al. '170 in no way teaches or suggests that NO may be synthesized by propionibacteria or by any of the processes described therein. Further, this reference does not disclose a dietary supplement which is a dehydrated preparation, a fermented liquid preparation or a unfermented liquid preparation. With regard to Hettinga et al. '170, Professor Ourry explains, in Paragraph 7 of the Declaration filed July 31, 2001, that "[n]o mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

As also noted above, Madec et al. '947 in no way teaches or suggests the release of nitric oxide by propionibacteria, and particularly not in a human or animal digestive tract, or a dietary supplement which is a dehydrated preparation, a fermented liquid preparation or an unfermented liquid preparation. With regard to Madec et al. '947, Professor Ourry explains, in Paragraph 8 of the Declaration filed July 31, 2001, that "[a]lthough considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not

invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

With regard to Balows et al., Appellants submit that this reference also fails to provide any suggestion of or incentive for synthesizing NO from propionibacteria. This is verified by Professor Ourry in Paragraph 6 of the Declaration filed July 31, 2001: "[I]t is clear that the book published by Balows et al. (1992) and cited by the Examiner does not reveal or show experimental data demonstrating that Propionibacteria are able to produce NO. Chapter 23 entitled 'The Denitrifying Prokaryotes,' is the only chapter considering the production of NO molecules by bacteria. The only mention of Propionibacteria in this chapter (Page 556, second paragraph) is given as: 'Whether a true respiratory utilization of nitrite by the fermentative Propionibacterium occurs, has been questioned; it may instead be a detoxification process (Kaspar, 1982). This sentence does not explicitly mean or even suggest that Propionibacteria are able to synthesize NO. Moreover, if the Kaspar reference is analyzed, then it appears that no experimental data concerning the NO synthesis by Propionibacteria is given; the author considered *sensu stricto* the synthesis of N_2O (nitrous oxide). Although it is well known that denitrifying bacteria have the metabolic apparatus to produce NO from nitrite, it cannot be deduced from the current knowledge that Propionibacteria share the same capacity. In chapter 37 of the Balows et al. reference, the genus Propionibacterium is described: the usual known habitat of such bacteria is limited to dairy products, while denitrifying bacteria are known to be telluric organisms. Therefore, in this book there is no direct or indirect evidence that can be used to suggest that Propionibacteria have the capacity to synthesize NO like denitrifying bacteria." (Citations omitted.) Furthermore, this reference provides no suggestion of or incentive for providing a dietary supplement being a dehydrated preparation, a fermented liquid preparation or an unfermented liquid preparation.

Therefore, Appellants submit, no combination of these three references may properly render either of claims 16 and 24 obvious to one of ordinary skill in the art under § 103. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used

against its teacher." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

Further, in traversing the appealed rejections Professor Ourry also states, in Paragraph 9 of the Declaration filed July 31, 2001, that, "[t]aken independently or even as a whole, none of the documents referred to by the Examiner provide any direct or indirect evidence to support the view that the invention proposed by applicants could be rendered obvious. None of them describes or even suggests (i) the synthesis of NO by Propionibacteria or uses a relevant reference to do so, or (ii) the use of these bacteria and their role in the digestive tract for NO accumulation. Overall, since the production of NO by Propionibacteria and its potential accumulation have never been described under general (i.e., before their consumption) or post-consumption conditions, it cannot be deduced that there is the potential for NO production within the digestive tracts of consumers without the knowledge provided by the applicants." Moreover, Professor Ourry submits, in Paragraph 10 of the Declaration, that none of the following original results obtained through a collaboration with Appellants and which constitute the basis of the invention, can be rendered obvious from the analysis of Hettinga et al. '170, Madec et al. '947 and/or Balows et al.:

i. Certain strains of Propionibacteria are able to produce significant amounts of NO under anaerobic conditions, which can further be accumulated in the surrounding medium.

ii. Synthesis of NO by Propionibacterium cultures does not involve the well known NO synthase pathway using arginine as a precursor, but another metabolic route using nitrate or nitride as a substrate.

iii. NO synthesis by Propionibacteria can use nitrate already present in a YEL growth medium and can be further increased by the supply of nitrate and nitrite.

iv. NO synthesis by Propionibacteria is increased at physiological body temperature (37°C) relatively to temperatures normally used in vitro for growing bacteria.

v. A comparison between different strains of Propionibacteria showed that not all strains are able to produce NO, several being devoid of any capacity for NO synthesis. Some specific strains have been characterized as being able to produce much more NO than other strains.

Additionally, Appellants submit that even if there were some suggestion or incentive for combining their teachings to yield the invention claimed in claim 16 or 24, nothing in the prior art references cited by the Examiner suggests the advantages to be derived from combining their teachings. "[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings." In re Sernaker, 702 F.2d 989, 995-96, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). Various advantages provided by the present invention(s), including those related to the health and energy-giving effects of nitric oxide, the means for administering a dosage thereof, and composition shelf life, are described in pages 1-4 of the specification.

For the above reasons, Appellants submit that no combination of the cited references may properly render the inventions claimed in claims 16 or 24 obvious under § 103, and respectfully request that these rejections now be reversed.

XIII. None of independent claims 19 and 29, and dependent claim 30, calling for a composition, or a method for making a composition, for use as an absorbable dietary supplement comprising more than 10^9 cells/gram propionibacteria or an amount of propionibacteria sufficient to release a physiologically significant amounts of nitric oxide into a human or animal digestive tract, and a quantity of bifidobacteria and/or lactic acid bacteria, is unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream and a culture of 0.002% lactobacillus bulgaricus, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 19, 29 or 30 is not expressly described in Hettinga et al. '170. This reference in no way teaches or suggests, let alone expressly describes, that NO may be synthesized by propionibacteria or by any of the processes described therein.

Nor is it necessary and inevitable that, in the disclosed cheesemaking process, the propionibacteria release a physiologically significant amount of NO into a human or animal digestive tract, and therefore Hettinga et al. '170 also fails to inherently describe each and every element as set forth in any of claims 19, 29 and 30. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 7 of the Declaration filed July 31, 2001: "No mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

For these reasons, Appellants submit that claims 19, 29 and 30 distinguish over Hettinga et al. '170 and, because each and every element set forth in any of claims 19, 29 and 30 is not expressly or inherently described in this reference, neither of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of these rejections.

XIV. Independent claim 19, calling for a composition for use as an absorbable dietary supplement comprising a sufficient quantity of propionibacteria and bifidobacteria and/or lactic acid bacteria, the composition capable of releasing a physiologically significant amount of nitric oxide into a human or animal digestive

tract, is not unpatentable under 35 U.S.C. § 102(b) over the disclosure of U.S. Patent No. 5,573,947 (Madec et al.), which discloses a culture medium in which propionic bacteria may be specifically counted, but which fails to teach or suggest the release of nitric oxide by propionibacteria, alone or in combination with bifidobacteria and/or lactic acid bacteria, particularly in a human or animal digestive tract.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Brothers, Inc. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that each and every element as set forth in claim 19 is not expressly described in Madec et al. '947. This reference in no way teaches or suggests, let alone expressly describes, the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract.

Nor is it necessary and inevitable that the propionibacteria being counted through use of the disclosed medium releases nitric oxide, and certainly not in a human or animal digestive tract, and therefore Madec et al. '947 also fails to inherently describe each and every element as set forth in claim 19. "The law requires that inherency may not be established by possibilities or probabilities. The evidence must show that the inherency is necessary and inevitable." Interchemical Corp. v. Watson, 145 F. Supp. 179, 182, 111 U.S.P.Q. 78, 79 (D. D.C. 1956), aff'd, 251 F.2d 390, 116 U.S.P.Q. 119 (D.C. Cir. 1958). The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient to establish inherency. Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991); In re Oelrich, 666 F.2d 578, 581 (C.C.P.A. 1981).

As Professor Ourry explains in Paragraph 8 of the Declaration filed July 31, 2001: "Although considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

For these reasons, Appellants submit that claim 19 distinguishes over Madec et al. '947 and, because each and every element set forth in claim 19 is not expressly or inherently described in this reference, none of these claims is anticipated by this reference under § 102(b). Appellants respectfully request reversal of this rejection.

XV. None of independent claims 19 and 29, and dependent claim 30, calling for a composition, or a method for making a composition, for use as an abs rbable dietary supplement comprising more than 10^9 cells/gram propionibacteria or an amount of propionibacteria sufficient to release a physiologically significant amounts of nitric oxide into a human or animal digestive tract, and a quantity of bifidobacteria and/or lactic acid bacteria, is unpatentable under 35 U.S.C. § 103(a) over a combination of the disclosures of U.S. Patent No. 4,379,170 (Hettinga et al.), which teaches a Swiss or Emmental cheese being prepared by a process which includes heat treating at 180°F for 30 minutes a skim milk concentrate, adjusting the temperature to 100°F and adding 0.05% proline, and fermenting the mixture with 80 ppm of protease and 6.6% inoculum of a 50/50 mixture of propionibacteria P16 and P20 (G-broth, 6.2 x 10^9 cells per gram of P16, 1.2 x 10^9 cells per gram of P20) for 5 hours, later mixing the fermentate with pasteurized cream and a culture of 0.002% lactobacillus bulgaricus, and cooking this mixture at 124°F for 20 minutes, but which fails to teach or suggest that NO may be synthesized by propionibacteria or by any of the processes described therein; U.S. Patent No. 5,573,947 (Madec et al.), which discloses a culture medium in which propionic bacteria may be specifically counted, but which fails to teach or suggest the release of nitric oxide by propionibacteria, alone or in combination with bifidobacteria and/or lactic acid bacteria, particularly in a human or animal digestive tract; and Balows et al., which teaches that propionibacteria are commonly used as starter cultures and can grow on media with nitrate, and that some bacteria are denitrifying bacteria which reduce nitrate to gaseous products comprising nitric oxide or nitrous oxide, but which fails to provide any direct or indirect evidence that can be used to suggest that propionibacteria have the capacity to synthesize NO.

"Obviousness cannot be established by combining teaching of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. Under section 103, teachings of references can be combined only if there is some suggestion or incentive to do so." ACS Hospital Systems, Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984) (emphasis provided) (citations omitted). Appellants submit that these references provide no suggestion or incentive for combining their teachings to yield the invention claimed in any of claims 19, 29 and 30

As noted above, Hettinga et al. '170 in no way teaches or suggests that NO may be synthesized by propionibacteria or by any of the processes described therein. With regard to Hettinga et al. '170, Professor Ourry explains, in Paragraph 7 of the Declaration filed July 31, 2001, that "[n]o mention of NO, or nitrogen monoxide, synthesized by these bacteria or even by any other process can be found in the description of this patent. This can be further supported by the fact that despite detailed chemical analysis of bacteria proliferation media within 14 examples, the precursor compounds needed for NO synthesis (nitrate or nitrite) have never been quantified or even considered. Moreover, it cannot be concluded by any means, from this document that the consumption of cheese produced by the described procedure will release in the digestive tract significant amounts of Propionibacteria, and even so, that they will produce NO."

As also noted above, Madec et al. '947 in no way teaches or suggests the release of nitric oxide by propionibacteria, particularly in a human or animal digestive tract. With regard to Madec et al. '947, Professor Ourry explains, in Paragraph 8 of the Declaration filed July 31, 2001, that "[a]lthough considering extensively in the introduction section all the potential use of Propionibacteria, this patent does not invoke or even suggest the production of NO by these bacteria and its potential use. Moreover, the different propositions of selective media for Propionibacterium counting given in this patent do not consider explicitly the nitrogen sources, and more specifically the substrate needed (nitrate or nitrite) for NO synthesis."

With regard to Balows et al., Appellants submit that this reference also fails to provide any suggestion of or incentive for synthesizing NO from propionibacteria. This is verified by Professor Ourry in Paragraph 6 of the Declaration filed July 31, 2001: "[I]t is clear that the book published by Balows et al. (1992) and cited by the Examiner does not reveal or show experimental data demonstrating that Propionibacteria are able to produce NO. Chapter 23 entitled 'The Denitrifying Prokaryotes,' is the only chapter considering the production of NO molecules by bacteria. The only mention of Propionibacteria in this chapter (Page 556, second paragraph) is given as: 'Whether a true respiratory utilization of nitrite by the fermentative Propionibacterium occurs, has been questioned; it may instead be a detoxification process (Kaspar, 1982). This sentence does not explicitly mean or even suggest that Propionibacteria are able to synthesize NO. Moreover, if the Kaspar reference is analyzed, then it appears that no experimental data concerning the NO synthesis by

Propionibacteria is given; the author considered *sensu stricto* the synthesis of N_2O (nitrous oxide). Although it is well known that denitrifying bacteria have the metabolic apparatus to produce NO from nitrite, it cannot be deduced from the current knowledge that Propionibacteria share the same capacity. In chapter 37 of the Balows et al. reference, the genus Propionibacterium is described: the usual known habitat of such bacteria is limited to dairy products, while denitrifying bacteria are known to be telluric organisms. Therefore, in this book there is no direct or indirect evidence that can be used to suggest that Propionibacteria have the capacity to synthesize NO like denitrifying bacteria." (Citations omitted.)

Therefore, Appellants submit, no combination of these three references may properly render any of claims 19, 29 and 30 obvious to one of ordinary skill in the art under § 103. "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed. Cir. 1983).

Further, in traversing the appealed rejections Professor Ourry also states, in Paragraph 9 of the Declaration filed July 31, 2001, that, "[t]aken independently or even as a whole, none of the documents referred to by the Examiner provide any direct or indirect evidence to support the view that the invention proposed by applicants could be rendered obvious. None of them describes or even suggests (i) the synthesis of NO by Propionibacteria or uses a relevant reference to do so, or (ii) the use of these bacteria and their role in the digestive tract for NO accumulation. Overall, since the production of NO by Propionibacteria and its potential accumulation have never been described under general (i.e., before their consumption) or post-consumption conditions, it cannot be deduced that there is the potential for NO production within the digestive tracts of consumers without the knowledge provided by the applicants." Moreover, Professor Ourry submits, in Paragraph 10 of the Declaration, that none of the following original results obtained through a collaboration with Appellants and which constitute the basis of the invention, can be rendered obvious from the analysis of Hettinga et al. '170, Madec et al. '947 and/or Balows et al.:

i. Certain strains of Propionibacteria are able to produce significant amounts of NO under anaerobic conditions, which can further be accumulated in the surrounding medium.

ii. Synthesis of NO by Propionibacterium cultures does not involve the well known NO synthase pathway using arginine as a precursor, but another metabolic route using nitrate or nitride as a substrate.

iii. NO synthesis by Propionibacteria can use nitrate already present in a YEL growth medium and can be further increased by the supply of nitrate and nitrite.

iv. NO synthesis by Propionibacteria is increased at physiological body temperature (37°C) relatively to temperatures normally used in vitro for growing bacteria.

v. A comparison between different strains of Propionibacteria showed that not all strains are able to produce NO, several being devoid of any capacity for NO synthesis. Some specific strains have been characterized as being able to produce much more NO than other strains.

Additionally, Appellants submit that even if there were some suggestion or incentive for combining their teachings to yield the invention claimed in claim 19, 29 or 30, nothing in the prior art references cited by the Examiner suggests the advantages to be derived from combining their teachings. "[P]rior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings." In re Sernaker, 702 F.2d 989, 995-96, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983). Various advantages provided by the present invention(s), including those related to the health and energy-giving effects of nitric oxide, the means for administering a dosage thereof, and composition shelf life, are described in pages 1-4 of the specification.

For the above reasons, Appellants submit that no combination of the cited references may properly render the inventions claimed in claims 19, 29 or 30 obvious under § 103, and respectfully request that these rejections now be reversed.

CONCLUSION

For the reasons advanced above, Appellants respectfully contend that the rejections of independent claims 13 and 20, and dependent claim 21, as being unpatentable over Hettinga et al. '170 or Madec et al. '947 under 35 U.S.C. §102(b), or over any combination of Hettinga

et al. '170, Madec et al. '947 and the disclosure of Balows et al. under 35 U.S.C. §103(a), is improper.

For the reasons advanced above, Appellants respectfully contend that the rejection of dependent claim 14, as being unpatentable over Hettinga et al. '170 or Madec et al. '947 under 35 U.S.C. §102(b), or over any combination of Hettinga et al. '170, Madec et al. '947 and the disclosure of Balows et al. under 35 U.S.C. §103(a), is improper.

For the reasons advanced above, Appellants respectfully contend that the rejections of independent claim 25, and dependent claims 15 and 26, as being unpatentable over Hettinga et al. '170 or Madec et al. '947 under 35 U.S.C. §102(b), or over any combination of Hettinga et al. '170, Madec et al. '947 and the disclosure of Balows et al. under 35 U.S.C. §103(a), is improper.

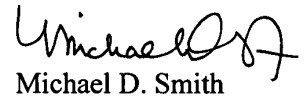
For the reasons advanced above, Appellants respectfully contend that the rejections of dependent claims 16 and 24, as being unpatentable over Hettinga et al. '170 or Madec et al. '947 under 35 U.S.C. §102(b), or over any combination of Hettinga et al. '170, Madec et al. '947 and the disclosure of Balows et al. under 35 U.S.C. §103(a), is improper.

For the reasons advanced above, Appellants respectfully contend that the rejections of independent claims 19 and 29, and dependent claim 30, as being unpatentable over Hettinga et al. '170 under 35 U.S.C. §102(b), or over any combination of Hettinga et al. '170, Madec et al. '947 and the disclosure of Balows et al. under 35 U.S.C. §103(a), is improper.

For the reasons advanced above, Appellants respectfully contend that the rejection of independent claim 19 as being unpatentable over Madec et al. '947 under 35 U.S.C. §102(b) is improper.

In the event Appellants have overlooked the need for an additional extension of time, payment of fee, or additional payment of fee, Appellants hereby petition therefor and authorize that any charges be made to Deposit Account No. 02-0385, Baker & Daniels.

Respectfully submitted,



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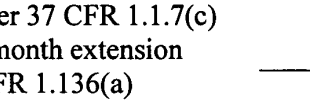
Enc. Appendix A (Claims on Appeal)
Check No. 052985 ($310.00) in payment of fee under 37 CFR 1.1.7(c)
Petition for two (2) month extension of time under 37 CFR 1.136(a)
Return postcard

CERTIFICATE OF MAILING

I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE AS FIRST CLASS MAIL IN AN ENVELOPE ADDRESSED TO: ASSISTANT COMMISSIONER FOR PATENTS, WASHINGTON, DC 20231, ON: September 7, 2001.

MICHAEL D. SMITH, REG. NO. 40,181
NAME OF REGISTERED REPRESENTATIVE



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September 7, 2001
DATE

APPENDIX A
Claims on Appeal in Serial No. 09/331,554

13. A composition for use as an absorbable dietary supplement for human and animal consumption comprising more than 10^9 cells/gram propionibacteria, said propionibacteria capable of releasing a physiologically significant amount of nitric oxide into the human and animal digestive tract for improving intestinal functions.

14. The composition according to Claim 13, wherein said propionibacteria, after cultivating for at least 72 hours in a Yeast Extract Lactate medium containing at least 550 μmol/liter of nitrate, is capable of releasing at least 5 μg of nitric oxide.

15. The composition according to Claim 13, wherein said composition is added to a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink.

16. A dietary supplement according to Claim 13, wherein said supplement is a preparation of the form selected from the list of dehydrated, fermented liquid, and unfermented liquid preparations.

19. A composition for use as an absorbable dietary supplement for human and animal consumption comprising a sufficient quantity of propionibacteria and one or more selected from the group consisting of bifidobacteria and lactic acid bacteria, said composition capable of releasing a physiologically significant amount of nitric oxide into the human and animal digestive tract.

20. A method for making a composition for use as a dietary supplement comprising the steps of:

providing a supply of propionibacteria; and

selecting an amount of propionibacteria sufficient to release physiologically significant amounts of nitric oxide into the human and animal digestive tract.

21. The method according to Claim 20, wherein said selecting step comprises selecting more than 10^9 cells/gram of propionibacteria.

24. The method according to Claim 20, further comprising the step of forming the dietary supplement into one of the group consisting of a dehydrated preparation, a fermented liquid preparation, or an unfermented preparation.

25. A method of making a food composition for use as a dietary supplement comprising the steps of:

providing a supply of propionibacteria;

selecting an amount of propionibacteria sufficient to release physiologically significant amounts of nitric oxide into the human and digestive tract;

providing a food product selected from a list including cheese, sources of dietary fibre, fermented milk, dessert cream, cake, and tonic drink; and

adding said propionibacteria to said food product.

26. The method of Claim 25, further comprising the step of selecting and inserting into a food preparation more than 10^9 cells/gram of propionibacteria.

29. A method of making a composition for use as a dietary supplement comprising
the steps of:

providing a supply of propionibacteria and at least one of the group of bifidobacteria and lactic acid bacteria;

selecting an amount of propionibacteria sufficient to release physiologically significant amounts of nitric oxide into the human and animal digestive tract.

30. The method according to Claim 29, wherein said selecting step comprises selecting more than 10^9 cells/gram of propionibacteria.